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Case Report

Pulmonary and testicular tuberculosis in one patient caused by *Mycobacterium tuberculosis* with different genotypes

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Abstract

Extrapulmonary tuberculosis (EPTB) accounted for 14% of 6.4 million cases of TB that were reported to WHO in 2017, and genitourinary TB (GUTB) is the second most common type of EPTB. The most common site of GUTB is the kidneys and testicular TB is relatively rare. The case of one patient with pulmonary and testicular TB caused separately by two different genotypes of *Mycobacterium tuberculosis* (*Mtb*) is further rare. Here, we present an unusual case of TB in which pulmonary TB (PTB) and testicular TB were caused by *Mtb* isolates with two different genotypes in a 91-year-old male patient from Zunyi, Guizhou Province of China. A better understanding of the mechanism by which a small number of tubercle bacilli are spread from the primary site of PTB to more distant parts/organs of the body, and what factors determine the potential EPTB site will provide us with new ways to prevent and control EPTB infections.

Key words: *Mycobacterium tuberculosis*; pulmonary and testicular tuberculosis; genotype.

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Introduction

Tuberculosis (TB), the leading cause of death from a single infectious agent in the world, typically affects the lungs (pulmonary TB, PTB), but can also affect other organs of the body including lymph nodes, the kidneys, genitourinary tract, bones and joints, meninges, the brain, or skin (extrapulmonary TB, EPTB). EPTB accounted for 14% of 6.4 million cases of TB that were notified by national TB programs (NTPs) and reported to WHO in 2017 [1]. EPTB is usually spread by a small number of tubercle bacilli entering the bloodstream or lymphatic channels from the site of PTB and spreading to more distant tissues and organs, and is often accompanied by PTB in HIV-infected patients [2]. Genitourinary TB (GUTB) is the second most common type of EPTB accounting for 30% to 40% of all EPTB cases and 15% to 20% of PTB cases in developing countries [3,4]. The most common site of GUTB is the kidneys from where the tubercle bacilli can spread to the rental tract, prostate and epididymis [3], and testicular TB is rare [5-9]. However, the case of one patient with pulmonary and genitourinary TB caused separately by two different genotypes of *Mycobacterium tuberculosis* (*Mtb*) is further rare. Here, we report such a case in a 91-year-old male patient from Zunyi, Guizhou Province of China.

Case Report

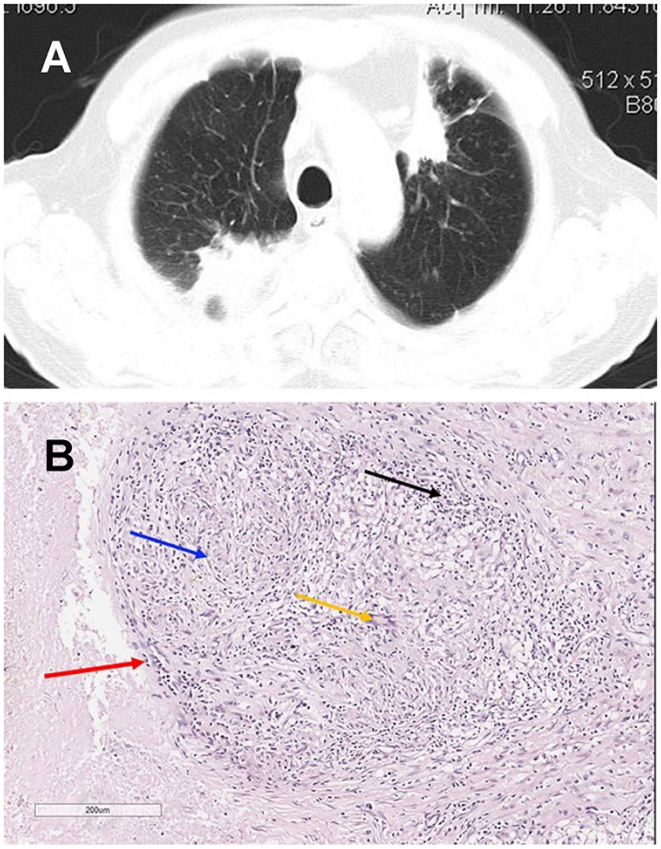
A 91-year-old Chinese man with PTB and testicular mass was referred to our hospital in July 2013. The patient came with symptoms of slight cough, mild fever (37.9ºC), and a few yellow phlegm. He had felt swelling and pain in his left scrotum for the past three months. Physical examination revealed that his both lungs had no positive signs for infection, but his left testis and spermatic cord were enlarged and tenderness. Computed tomography (CT) scan of the chest revealed large exudative lesions and multiple fibrosis lesions in the upper lobes of both lungs suggesting a secondary PTB (Figure 1A). The patient's sputum culture was positive for *Mtb* and scrotal ultrasound scan revealed a solid structure with low heterogeneous echo in the left testis and bilateral testicular hydrocele. His left testis was removed during a radical orchidectomy, and gross examination of intraoperative testicular tissues showed multiple caseous necrotic materials. Pathological and histological examinations of testicular tissue sections revealed tuberculosis granulomas in the testis (Figure 1B). Culture of the diseased testicular tissue was positive for *Mtb*, and therefore the patient was

diagnosed with secondary PTB in both lungs and testicular TB.

Mtb isolates collected from cultures of sputum specimens and testicular tissues were used for drug susceptibility testing (DST) against four first-line antituberculosis drugs (isoniazid, rifampicin, streptomycin and ethambutol) as described previously [10]. Results showed that *Mtb* isolates from the lungs and testicular tissue were susceptible to four first-line antituberculosis drugs. Based on the DST results, a daily treatment regimen with isoniazid (300 mg), rifampicin (450 mg), and ethambutol (750 mg) was initiated for the patient immediately after the diagnosis and continued for two months; followed by isoniazid (300 mg daily) and rifampicin (450 mg daily) for the next nine months. Patient's symptoms abated and his sputum smears for acid-fast bacilli were negative after the treatment.

To understand the relationship between pulmonary and testicular TB, we carried out molecular typing of genomic DNA samples extracted from clinical isolates from the sputum and testicular specimens by using the Multiple Locus Variable-number tandem-repeat Analysis (MLVA) and spacer oligotyping (spoligotyping) methods. Genomic DNA extracted from the standard strain H37Rv (provided by the Chinese Center for Disease Control and Prevention) was used as a control and the BioNumerics 5.0 software (Applied Maths) was used for the DNA fingerprinting and polymorphism analysis. The MLVA genotypes were determined to be 322722533324582 and 322322533324582 for clinical isolates from the sputum and testicular specimens respectively. Results from spoligotyping showed that *Mtb* isolate from the sputum was clustered to a new orphan genotype whereas *Mtb* isolate from the testicular tissue was clustered to the T1 family. In brief, genotyping results indicated that the genotype for *Mtb* isolate from the PTB was different from that from the testicular TB in this particular patient.

Figure 1. (A) Chest CT scan image showing large pulmonary exudative lesions and multiple fibrosis lesions in the upper lobes of both lungs. (B) Testicular tissue section showing granulomatous inflammation: tuberculous granuloma (red arrow), epithelioid cells (blue arrow), lymphocytes (black arrow), and multinucleated Langhans-type giant cells (yellow arrows) (H and E stain ×200).



Discussion

EPTB can develop in many parts/organs of the body and usually present with a variety of clinical manifestations. Risk factors for EPTB included age ≥45 years, female gender, HIV-positive, and end-stage rental disease [11]. Genitourinary TB is the second most common type of EPTB and the most common site of GUTB is the kidneys, but testicular TB is occurring in about 3% of GUTB [5]. Although culture of *Mtb* remains the gold standard for diagnosis of EPTB, it is sometimes difficult to obtain specimens from patients of EPTB for the *Mtb* culture test and the culture as well as molecular methods may give negative results [6,7]. Therefore, accurate diagnosis of EPTB poses a major challenge due to its atypical presentation and should be based on clinical manifestations corresponding to EPTB, histopathological evidence, or at least one positive for *Mtb* (smear, culture or molecular test) [12].

Testicular TB could be easily misdiagnosed as testicular tumors, as isolated tuberculous epididymo-orchitis cases did mimic testicular tumors particularly in patients without systemic symptoms associated with active PTB such as cough, weight loss, fever, and chest pain [6-9]. Consequently, endoscopic, microscopic and histopathological examinations after the operation are important for precise diagnosis of testicular TB, because *Mtb* may not be isolated from every testicular specimen [6]. Different imaging methods used in diagnosing EPTB and monitoring treatment response were compared in a recent review article, which included CT, MRI (magnetic resonance imaging), and

^{18}F-FDG PET-CT (^{18}F-fluorodeoxyglucose position emission tomography-computed tomography) [13]. These imaging methods have the potential to play a more important role in the early detection of TB in most parts of the body, differentiation of various manifestations, assessment of treatment responses, and evaluation of disease burdens in patients with TB, especially EPTB [13,14].

Because EPTB often coexist with PTB, it is generally believed that EPTB occurs when PTB spread from the lungs to other parts of the body. Therefore, both PTB and EPTB should originate from the same strain of *Mtb* and have the same genotype. In a few reported cases of patients with both PTB and testicular TB, results of molecular typing were missing [5,15]. In this study, *Mtb* was successfully isolated from sputum and testicular specimens of the same patient, which provided evidence-based diagnosis of pulmonary and testicular TB and demonstrated that PTB and testicular TB were caused by *Mtb* isolates with different genotypes. Spoligotyping results showed that *Mtb* isolates from the sputum and the testicular tissuewere clustered to a new orphan genotype and the T1 family respectively. Therefore, we cannot simply assume that the testicular TB is always spread from the same strain of *Mtb* which initiated the primary infection in the lungs of the patient. Although two *Mtb* strains from the sputum and the testicular tissue had different genotypes, both were susceptible to four first-line anti-TB drugs, which made it simple to select an appropriate treatment regimen.

Mtb isolate from the testicular tissue in our case was clustered to the T1 family, which is the same as the family with the highest frequency found by molecular typing of *Mtb* isolated from smear-negative EPTB patients in central Ethiopia [16]. The single nucleotide polymorphism (SNP)-based genotyping of 1,282 PTB and 132 EPTB patients in Thailand showed that sequence types (STs) 10 and 22 were found more frequently in EPTB patients (31.8% for ST10 and 10.6% for ST22) than in PTB patients (14.1% for ST10 and 5.5% for ST22) [15]. Nevertheless, ST19 and ST24 were found more frequently in PTB patients (13.9% for ST19 and 8.1% for ST24) than in EPTB patients (6.8% for ST19 and 4.5% for ST24) [17]. Spoligotyping of 113 bone and joint TB cases reported in China showed that 87.6% (99/113) isolates were identified as Beijing genotype [18]. Results from these molecular typing studies suggest that different genotypes of *Mtb* may have different potential to infect different organs of the body or spread from the lungs to other organs of the body.

Conclusion

This case report demonstrates that pulmonary TB and testicular TB can be caused by *Mtb* isolates with different genotypes in one patient, indicating that *Mtb* isolates with different genotypes may have different potential to spread from the primary site of infection in the lungs to other parts/organs of the body such as the testis. A better understanding of the mechanism how a small number of tubercle bacilli are spread from the site of PTB to more distant tissues and organs, and what factors determine the potential EPTB site will provide new ways to prevent and control EPTB infections.

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Author contributions

YL carried out the experiments, organized the data and prepared the manuscript. LC supervised this study. LC and HZ revised the manuscript. All authors contributed to analysis and interpretation of the data, read and approved the final version of the manuscript.

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Conflict of interests: YL and LC declare no conflicts of interest. HZ is employed by and has shares in Z-BioMed, Inc., which is involved in infectious disease research.